

BONE MARROW NECROSIS

Layla A. Al-Gwaiz, MD, FCAP

Patchy and focal bone marrow necrosis (BMN) is a relatively common finding in routine bone marrow (BM) biopsy specimens,² however, severe BMN is rarely diagnosed in living patients and is more frequently diagnosed in autopsy BM.²⁻⁴ BMN has been described in a variety of neoplastic and non-neoplastic diseases.^{2,3,5-10} This is a retrospective analysis of consecutive BMN biopsies received over the last five years to assess the incidence of BMN in antemortem biopsies and the diseases associated with it.

Materials and Methods

The bone marrow trephine biopsies received between June 1991 and May 1996 at the Hematology Section, Department of Pathology at King Khalid University Hospital, Riyadh, Saudi Arabia, were retrospectively reviewed. The biopsies were obtained from the posterior iliac spine with a Jamshidi needle and stained with hematoxylin and eosin stain. The biopsies were evaluated for the presence of necrosis. Giemsa-stained BM aspirates obtained from the cases with necrosis were also assessed for evidence of necrosis, e.g., the presence of necrotic cells and necrotic eosinophilic materials for correlation with the biopsy findings.

The records of patients with BMN were reviewed for age, sex, diagnosis and the clinical and laboratory features.

Results

We reviewed 1014 consecutive BM biopsies: 85 were diagnosed as acute myelocytic leukemia (AML), 83 as acute lymphocytic leukemia (ALL), 43 as non-Hodgkin's lymphoma (NHL), 17 as metastatic carcinoma, and 12 as Hodgkin's disease (HD). There were 16 cases of BMN, with an incidence of 1.6%. Table 1 shows the

TABLE 1. Incidence of bone marrow necrosis in relation to diagnosis.

Diagnosis	Biopsies with necrosis (no./cases)	Incidence
Hodgkin's disease	3/12	25%
Metastatic carcinoma	2/17	11.8%
Acute lymphocytic leukemia	7/83	8.4%
Acute myelocytic leukemia	2/85	2.4%
Non-Hodgkin's lymphoma	1/43	2.4%

incidence of BMN in relation to the diagnosis. The clinical and laboratory features are shown in Table 2.

The BM biopsies showed variable necrosis between 30%-100% of the size of the biopsy (Figure 1). The necrosis included both the hematopoietic tissue and bony matrix. The corresponding BM aspirates revealed individual necrotic cells in ten cases and homogenous eosinophilic necrotic material was seen only in three cases, in spite of extensive necrosis in the corresponding biopsies.

Discussion

Severe BMN is a relatively infrequent diagnosis in routine BM specimens. It is more commonly encountered at autopsy.²⁻⁴ The incidence of BMN is variable (0.5%-3%). Vesterby and Jensen⁴ reported BMN to be 6.5% in autopsies of leukemic patients, while Dunn et al.¹¹ reported an incidence of 0.37% in consecutive BM aspirates performed alone or with biopsies. In our cases, the incidence was 1.6% of consecutive BM biopsies. In about six of our cases, no significant necrosis was detectable in the aspirate, despite extensive necrosis in the biopsies. This could be explained by variation in the extent of necrosis in different sites.

All our cases except for one were associated with neoplastic diseases. The highest incidence was in HD (25%), followed by metastatic carcinoma (11.8%), and ALL (8.4%). Six of the seven cases of ALL were on initial presentation, while the seventh was associated with relapse. In all of these cases, areas with viable blasts were present and hence the diagnosis was not obscured. In one case, there was complete necrosis of the marrow and no malignancy or infection was detected despite thorough

From the Hematology Section, Department of Pathology, King Khalid University Hospital, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al-Gwaiz: Consultant Hematologist and Assistant Professor, Hematology Section, Department of Pathology, King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

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TABLE 2. Associated diseases, clinical symptoms, hematological parameters and serum LDH and AP levels.

Case #	Age (yrs)	Sex (M/F)	Associated disease	Bone pain	Fever	Hb (g/L)	Platelet count (x10 ⁹ /L)	WBC (x10 ⁹ /L)	Serum LDH	Serum AP
1	5	M	ALL, relapse	+	+	90	43	8.2	NA	↑
2	24	F	AML, postchemotherapy	+	-	102	20	8.2	↑	NA
3	15	M	AML	+	+	124	587	4.5	NA	NA
4	30	F	ALL	+	+	85	165	10.9	NA	NA
5	21	M	ALL	+	+	127	73	20.4	↑	↑
6	28	M	ALL	+	+	94	56	11	N	↑
7	80	M	Metastatic carcinoma	-	-	93	155	6.3	NA	NA
8	27	M	HD	-	-	92	276	2	↑	↑
9	23	M	ALL	+	+	133	135	8.9	NA	↑
10	60	M	HD	-	-	94	162	4.8	NA	NA
11	19	F	ALL	+	+	106	107	1.6	NA	↑
12	26	M	Metastatic carcinoma	+	-	85	18	5.3	↑	↑
13	30	F	NHL	-	+	93	23	2.3	↑	N
14	14	F	HD	-	-	119	225	8.6	↑	↑
15	25	F	ALL	-	+	50	18	295	↑	↑
16	28	M	No etiology identified	+	+	104	48	5	↑	↑

ALL=acute lymphocytic leukemia; AML=acute myelocytic leukemia; HD=Hodgkin's disease; NHL=non-Hodgkin's lymphoma; Hb=hemoglobin; LDH=lactate dehydrogenase; AP=alkaline phosphatase; NA= not available; N=normal; ↑=increased.

clinical and histological investigation. About 133 cases of BMN have been described in the literature.^{2,3,5-10} Most of these had leukemia (39%), ALL in particular (28.6%), followed by metastatic carcinoma (21.8%), lymphoma (15%), infections (6.8%),¹² and sickle cell disease (6.8%).¹³ In some cases, no known etiology was identified.^{6,14,15} In acute leukemia, BMN has been described at presentation, following chemotherapy or during relapse.^{8,14,15} In two children reported by Niebrugge and Benjamin,¹⁶ BMN preceded the development of ALL. Seven of our nine leukemia cases occurred at presentation.

Our cases seem to show a similar pattern of association with neoplastic diseases. None of our cases was associated with infections or sickle cell disease. This is probably because BM examination is not commonly performed in these patients. It seems that malignant diseases are common in living patients, while infections are more common in autopsies.^{10,17}

The most commonly described clinical findings of BMN are bone pain and fever.^{2,3,5,6,18} The majority of our cases had a similar clinical picture. Laboratory findings in BMN are characterized by pancytopenia,^{18,19} a leukoerythroblastic blood picture,^{11,18} and elevated serum lactate dehydrogenase (LDH) and alkaline phosphatase (AP) levels. Almost all our patients had anemia and half had thrombocytopenia. Leukoerythroblastic blood picture was present in three patients, two of whom had metastatic tumors, while the third was of an unidentified etiology. The last case also showed microangiographic features, as previously described in some cases.¹⁸ Biochemical tests were significant for elevated serum AP in 10 of 11 cases, and LDH in eight of nine cases. Both enzymes, and in

particular, LDH, are commonly elevated in neoplastic diseases, particularly in leukemias and lymphomas.

Most of the cases of BMN are diagnosed on BM examination. The histopathologic diagnosis of BMN is based on the demonstration of widespread necrosis of hematopoietic elements in BM trephine biopsies. It appears as eosinophilic material and should be differentiated from aspiration artifact, serous fat atrophy and amyloid deposition. BM aspirates may show necrosis manifested by individual necrosis and in some cases by the presence of homogenous eosinophilic material. The necrotic BM may resist aspiration, resulting in dry tap.²⁰ This further emphasizes the role of trephine biopsies in diagnosis. In our cases, ten cases showed individual necrotic cells. However, the eosinophilic material previously described was seen in only three cases, despite extensive necrosis. This may be related to the site of the aspirate.

The prognosis of BMN is generally considered very poor.^{2,5,6} However, this may be a reflection of the underlying life-threatening malignant diseases. It appears that when milder degrees of BMN are present, the prognosis depends primarily on the underlying disorder, whereas severe BMN is associated with an unfavorable clinical outcome.^{3,6,1} The association of BMN with poor prognosis, especially in children with ALL, has been disputed.¹⁹

BMN is an uncommon entity in BM specimens from living patients. It is usually associated with malignant

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FIGURE 1. Bone marrow trephine biopsy, showing bone marrow necrosis (H&E, 100x).

diseases. It may precede or be diagnosed simultaneously with these disorders. In a few cases, it may obscure the diagnosis. Hence, cases of necrosis should be investigated for the presence of an associated malignancy by obtaining adequate, and if needed, repeated biopsies. Leukemia, lymphoma and metastatic carcinoma are the most common causes of BMN in antemortem specimens.

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